Clinical Forum

Audiologic Findings in a Set of Fraternal Twins with CHARGE Association

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Abstract

CHARGE association refers to a constellation of congenital malformations of unknown etiology that includes ocular Coloboma, Heart defects, choanal Atresia, Retarded growth/development, Genital hypoplasia, and Ear anomalies and/or hearing loss. This paper discusses audiologic results in a set of fraternal twins with a diagnosis of CHARGE. Both infants exhibit external ear defects and audiologic patterns characteristic of CHARGE and demonstrate the variable and often asymmetric findings associated with this disorder. Early identification and evaluation are imperative for appropriate audiologic management of individuals with a diagnosis of CHARGE and for persons with CHARGE-like anomalies.

Key Words: CHARGE, coloboma, choanal atresia, hearing disorder, teratogen, congenital anomalies, twins

The term, CHARGE association, was first introduced by Pagon et al (1981) to characterize individuals who manifest a specific pattern of multiple congenital malformations. The CHARGE acronym refers to the most common anomalies of ocular Coloboma, Heart defects, choanal Atresia, Retarded growth and/or development, Genital hypoplasia, and Ear anomalies and/or hearing loss. A diagnosis of CHARGE is made when at least four of these six abnormalities are present. Renal disorders and facial palsy are observed almost as frequently as the six primary features and can also assist in confirming the diagnosis of CHARGE (Oley et al, 1988).

The etiology of CHARGE remains unknown, although embryologic events corresponding to the observed anomalies indicate an arrest in development approximately 25 to 45 days postconception (Pagon, et al, 1981; Duncan et al, 1988; Kaplan, 1989). While the majority of reported cases have been sporadic, both recessive and dominant patterns of inheritance have been cited (Mitchell et al, 1985; Davenport, Hefner and Mitchell, 1986; Oley et al, 1988; Blake et al, 1989). Chromosome karyotype studies carried out to date, however, fail to demonstrate any aberration related to the CHARGE association (Ho et al, 1975; Dobrowski et al, 1985; Oley et al, 1988).

A previously unidentified teratogenic agent could also affect embryologic development during the above stated critical period to produce the constellation of defects that characterize CHARGE. For example, eye, ear, choanal, and heart anomalies have been reported in thalidomide embryopathy (Smithells, 1973), and eye and heart defects have been noted following the use of diphenylhydantoin (Bartoshesky et al, 1982). Grix (1982) described CHARGE-like malformations in infants of diabetic mothers, and Siebert et al (1985) suggested that the facial and cardiac anomalies present in CHARGE, Fetal Alcohol Syndrome (FAS), and DiGeorge syndrome (absence of thymus and parathyroid glands) may have a related environmental origin. Nevertheless, no documented teratogens can yet account for the association of defects specific to CHARGE.
OTOLGIC AND AUDIOLOGIC FEATURES

The spectrum of otologic and audiologic features in CHARGE range from negligible to quite severe. The “E” in CHARGE, as suggested by Pagon et al (1981), initially referred to external ear malformations and/or hearing loss. Detailed reports by various investigators, however, reveal the presence of abnormalities throughout the peripheral, and possibly even the central, auditory systems (Davenport, Hefner, and Mitchell, 1986; Thelin et al, 1986; Wright et al, 1986; Guyote et al, 1987).

Davenport, Hefner, and Thelin (1986) noted that the morphological defects of the external ear are so distinctive that a tentative diagnosis of CHARGE can be made on the basis of patterns of ear shape alone. Characteristic features include a triangular concha, discontinuity between the antihelix and antitragus, “snipped-off” helical fold, small or absent ear lobes, cup-shaped ears, and/or short wide pinnae. These external ear defects may be bilateral or unilateral, and are often asymmetrical. Interested readers are referred to pages 139 to 141 of Davenport, Hefner, and Thelin (1986) for photographs of external ear anomalies specific to CHARGE.

Histologic examination of the temporal bones of individuals with a diagnosis of CHARGE has revealed multiple malformations throughout the middle and inner ears. Wright et al (1986) studied four temporal bones obtained from two cases of CHARGE at autopsy. Significant defects were present in all four specimens, including ossicular anomalies, absence of the stapedius muscle, absence of the oval window, aberrations of the facial nerve, Mondini-type malformation of the cochlea, and numerous malformations of the vestibular apparatus. Guyote et al (1987) noted similar defects in the temporal bones of a 7 1/2-month-old infant, and designated this unique pattern of findings as “CHARGE displasia of the temporal bone” (p. 324).

Evidence of auditory brainstem disorder was reported in one case of CHARGE by Thelin et al (1986). Auditory Brainstem Response Audiometry (ABR) assessment yielded normal absolute component wave V latencies at 10 and 30 dB nHL, with an abnormal prolongation in latency at 70 dB nHL. In addition, component wave V demonstrated an excessive latency shift when stimulus rate was increased from 11.1 to 77.7 clicks/second. To date, however, the question of central auditory dysfunction in CHARGE remains unsubstantiated by other research reports.

Hearing sensitivity loss has been reported in 21 percent to 95 percent of individuals with CHARGE (Pagon et al, 1981; Thelin et al, 1986; Oley et al, 1988; Kaplan, 1989). It is possible that the prevalence of hearing loss has been underestimated due to factors such as death prior to audiologic assessment, difficulty in acquiring valid behavioral audiology due to developmental delay, and inclusion of individuals in studies who were examined prior to the routine use of ABR audiometry as a means of hearing assessment (Pagon et al, 1981; Duncan et al, 1988).

With the exception of a comprehensive report by Thelin et al (1986), specific discussions of hearing loss related to CHARGE association have been limited and lacking in detail. Pagon et al (1981) reported that hearing loss is characteristically sensorineural in nature and ranges from mild to profound. In contrast, Thelin et al (1986), as well as other investigators (Kaplan, 1985; Davenport, Hefner, and Mitchell, 1986; Blake et al, 1990), have demonstrated a high incidence (30 to 93%) of conductive and mixed hearing sensitivity loss.

Thelin and colleagues (1986) proposed the existence of a hearing loss specific to CHARGE that is characterized by a (1) primarily low frequency or flat conductive hearing loss resulting from middle ear anomalies, (2) predominantly high-frequency sensorineural loss related to cochlear anomalies, (3) conductive loss related to middle ear effusion, and (4) possible progressive hearing loss (conductive, sensorineural, or mixed). The audiometric configuration considered unique to CHARGE is thus a “wedge-shaped” pattern in which there is a low frequency conductive loss with a concomitant high-frequency sensorineural component. The bone conduction threshold curve often slopes downward from low to high frequencies, while the air conduction threshold curve is flat. Degree of hearing loss varies, although it is typically moderately severe or greater and is frequently asymmetrical.

CASE REPORTS

The following reports discuss the audiologic evaluation and management of a set of fraternal twins with CHARGE association. They were born by repeat C-section at 34 weeks...
gestation due to premature onset of labor and failure to progress, and were admitted to the Neonatal Intensive Care Unit (NICU) at a local hospital. Neither a family history of hearing sensitivity loss nor anomalies associated with CHARGE were reported. In accordance with neonatal hearing screening program criteria, the infants were identified as at-risk for hearing loss due to the external ear defects described below. Initial assessment with ABR Audiometry was carried out at 2 weeks of age.

**Twin A**

HS was a 2,170 gram black female with APGAR scores of 6 at 1 minute and 7 at 5 minutes. She was slightly arocyanotic with delayed cry, but improved rapidly with stimulation. Physical examination revealed a low-birthweight infant with mildly decreased tone and obvious otologic and visual defects. She had asymmetric facies with pinnae that were low-set and triangular in shape. The helix had a “snipped-off” appearance and the antihelix was poorly defined. Ocular malformations included optic nerve coloboma on the right and iris and choroidal coloboma on the left. A heart murmur was present, and an echocardiogram and chest roentgenography revealed a patent ductus arteriosus and moderate cardiomegaly. ECG demonstrated left atrial and ventricular enlargement. CT scan, microscopic otoscopy, and chromosome karotype were normal.

Figure 1 illustrates the initial ABR tracings acquired to alternating air- and bone-conducted click stimuli (rate 11.1/sec; bandpass filter 30 to 3000 Hz) at 2 weeks of age in the NICU. The overall pattern of results indicated a moderate to moderately severe hearing sensitivity loss in the 1000 to 4000 Hz frequency region in the right ear, and a severe hearing loss for the above stated frequency range in the left ear. There was also evidence of a significant conductive component in the right ear. A replicable air-conduction response was present in the right ear at 70 dB nHL, but no response was obtained from the left ear at maximum equipment intensity limits of 95 dB nHL. A bone-conducted ABR signal generated a reliable waveform at 35 dB nHL with right mastoid placement. No response was observed to unmasked left mastoid stimuli at a maximum signal intensity of 45 dB nHL. The lack of a need to mask the right ear during left ear bone conduction testing was not unexpected as it has been our experience that there is approximately a 25 to 30 dB interaural attenuation for bone-conducted ABR stimuli in neonates. Brainstem transmission time could not be calculated due to the lack of a replicable component wave I. The interpeak interval between component waves III and V, however, was within age-appropriate normal limits.

Follow-up ABR assessment at 3 months of age yielded results consistent with those of the initial evaluation. Behavioral Observation Audiometry (BOA) in soundfield resulted in an eye-widening reaction to speech at 85 dB HL. The infant also ceased sucking in response to a 70 dB HL broadband noise stimulus. Attempts to carry out immittance audiometry were unsuccessful due to the child’s active behavior. She was referred to the Regional Day School Program for the Deaf for hearing aid fitting, continued audiologic management, and educational placement in a parent-infant stimulation program.

**Twin B**

DS was a 2,230 gram black male with APGAR scores at 8 at 1 and 5 minutes. Ears were low-set and triangular in shape, characterized by incomplete helical folds and a poorly defined antihelix. Ocular abnormalities included microphthalmia of the right eye, cataract of the
left eye, bilateral iris and choroidal coloboma, and bilateral retinal detachment. A significant cardiac murmur was present, and echocardiogram showed a moderate sized ductus arteriosus and probable subaortic stenosis. The possibility of pulmonic valve stenosis was also addressed but not confirmed at the time of discharge. CT scan, microscopic otoscopy, and chromosome karotype were unremarkable.

Initial ABR tracings, obtained in the NICU at 2 weeks of age, are shown in Figure 2. The pattern of results suggested a moderate hearing sensitivity loss in the 1000 to 4000 Hz frequency region in the right ear and a severe loss for this frequency range in the left ear. As noted for twin A, there was evidence of a substantial conductive component in the right ear. A replicable air conduction response was obtained from the right ear at 60 dB nHL, but no response was observed from the left ear at maximum equipment intensity limits (95 dB nHL). Bone conduction ABR yielded a reliable waveform at 25 dB nHL with right mastoid placement, although no response was obtained for bone conducted signals when the oscillator was placed on the left mastoid at 45 dB nHL (maximum limits). As discussed previously, masking was not employed during bone-conduction testing. Interpeak latency intervals were within normal limits for the child’s gestational age and showed no evidence of auditory brainstem pathway disorder.

Follow-up audiologic testing was carried out at 3 months of age. ABR results were in agreement with those of the previous assessment. BOA yielded a quieting response to a 500 Hz pulsed tone signal introduced in soundfield at 50 dB HL, as well as a crying reaction to a 50 dB HL broadband noise stimulus. Bilateral acoustic immittance measures were characterized by normal Type A tympanograms and absent uncrossed acoustic reflexes as screened at 1000 Hz. The child was referred to the Regional Day School Program for the Deaf for hearing aid fitting, audiologic management, and placement in a parent-infant stimulation program.

Management

The twins were fitted initially with bone-conduction hearing aids as their anomalous ears would not accommodate an earmold. Significant benefit from the amplification was reported by the Regional Day School Program. HS responded to speech presented in soundfield at 40 dB HL and DS responded to speech as low as 25 dB HL. These aided responses were in good agreement with the bone-conducted ABR thresholds obtained at the hospital’s audiology service at 2 weeks and at 3 months of age.

Figure 3 represents the right ear aided audiograms received from the educational program when the twins were 2 years of age. By age 2, their ears had increased in size and had thus permitted the audiologist to discontinue use of the bone-conduction hearing aids and to fit the children with behind-the-ear power aids. The audiograms, which were reported to reflect minimal response levels, showed a rising configuration with aided pure-tone averages of 50 dB for HS and 57 dB for DS. Speech awareness thresholds (SAT) for each child were 40 dB HL.

Figure 3 Right ear aided (Unitron EIPL) audiogram for HS at 2 years of age (left) and right ear aided (Oticon E28P) audiogram for DS at 2 years of age (right).
When the twins were approximately 3 years of age, parent-infant program personnel reported that both children exhibited poorer behavioral responses to auditory stimuli than observed previously. Attempts by the program's audiologist to obtain reliable ear-specific pure-tone audiograms were unsuccessful due to the twins' significant developmental delay. To assist in educational programming and explore the possible elevation in hearing thresholds, HS and DS were referred for repeat ABR assessments at 3 years, 5 months of age. Results of these evaluations are illustrated in Figures 4 and 5.

A degradation in waveform morphology and obvious elevation in peripheral hearing sensitivity had occurred since previous ABR testing. Right ear air-conduction thresholds increased from 75 to 85 dB nHL and from 70 to 85 dB nHL for HS and DS, respectively. Right mastoid bone conduction responses, however, were consistent with prior test results and continued to indicate essentially normal cochlear sensitivity in the frequency region stimulated by the bone-conducted click signal. As noted previously, there was no response from the left ear of either twin for air-conducted signals, nor was a response obtained from DS with left mastoid bone-conduction stimuli. Left mastoid bone-conduction testing was not completed for HS, as she awoke and sedation could not be readministered per physician request.

The elevation in air-conduction hearing sensitivity as measured by ABR was not related to active middle ear disease. Both children were examined by an otolaryngologist prior to ABR assessment, and well ventilated middle ears without obvious pathology were observed. The possibility of a progressive hearing sensitivity loss must therefore be considered, a finding not inconsistent with that noted by other investigators (Davenport, Hefner, and Mitchell, 1986; Thelin et al, 1986). For example, Thelin and colleagues (1986) reported a probable progression of conductive and/or sensorineural hearing loss components in approximately 47 percent of the CHARGE population studied.

Since the elevation in the twins' ABR thresholds was limited to air-conduction responses, one may infer that, for some unexplained reason, the conductive hearing loss component progressed. It is possible, however, that the sensorineural component actually increased. Weber (1983) compared the acoustic spectra for air-conducted and bone-conducted click stimuli and demonstrated a significant difference in energy concentration. An air-conduction click

![Figure 4](image-url) Air- and bone-conduction ABR tracings for HS at age 3 years, 5 months. Note the degradation in waveform morphology and elevation in air-conduction threshold since the initial evaluation (see Figure 1).

![Figure 5](image-url) Air- and bone-conduction ABR tracings for DS at age 3 years, 5 months. Note the degradation in waveform morphology and elevation in air-conduction threshold since the initial assessment (see Figure 2).
generates a significant concentration of energy in the 3000 Hz region, while the bone-conduction click generates peak energy around 1000 Hz, with no energy at 3000 Hz. As a result, sensorineural sensitivity could increase for frequencies above 1000 Hz and produce an elevation in the air-conducted click threshold without a concomitant increase in the bone-conduction threshold. Until we are able to obtain reliable, ear-specific pure-tone audiograms for HS and DS, it will be difficult to define precisely the conductive and sensorineural hearing loss components.

**COMMENT**

This paper apparently represents the first audiological report of fraternal twins with CHARGE association. The fact that they are not monozygotic lends credence to the possibility of an undefined teratogenic etiologic factor, although a recessive pattern of inheritance cannot be ruled out. Both children possess external ear malformations and audiometric findings typical of those described by Davenport, Hefner, and Mitchell (1986) and Thelin et al (1986) as characteristic of CHARGE. Of interest in this report, however, is the similarity in audiometric results between the twins. Hearing sensitivity as defined by ABR click stimuli demonstrated a probable primarily conductive hearing loss in the right ear, while left ear results indicated a severe, primarily sensorineural or mixed deficit. Final ABR testing supports the possibility of a progressive hearing loss in CHARGE as suggested by Thelin et al (1986). These findings serve to confirm the asymmetric and variable nature of hearing impairment related to CHARGE, and emphasize the importance of early and frequent audiological management. It is imperative that infants with a diagnosis of CHARGE or with anomalies characteristic of the CHARGE association receive immediate audiological assessment to achieve effective habilitation of hearing loss often observed with this disorder.

**REFERENCES**


